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TITLE: Development of a Hand Held Thromboelastograph

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CONTRACTING ORGANIZATION:

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14. ABSTRACT

The project objective is to develop a hand-held, ultra-portable thromboelastograph, ready for submission for FDA 510(k) clearance for clinical assessment of platelet function. Entegrion has designated the device as the *Portable Coagulation Monitor* (PCM).

As requested by Contractor, the completion date for this project was extended by one year. This report summarizes progress to date at the end of year three (Y3). The overall summary of the Project Timeline is:

1- V 2.0 Prototype Design, Testing, Validation – months 1-38

2- Formal definition of Design Requirements & Specification – Months 13-15

3- Product Design & Development – Months 16-38

4- Certification Testing and subsystem design corrections if needed – months 38-47

5- Manufacturing Documentation – Months 30-47

6- FDA 510(k) Submission – Month 48

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Introduction

Military Relevance

Trauma is known to induce hemostatic disorders such as trauma-induced coagulopathy (TIC), which evolves rapidly during the first few hours following injury. Commercially available devices for measuring blood-clotting status have many limitations that render them generally unsuitable for use in forward military treatment facilities and particularly during patient transport. These devices (Haemonetics' thrombelastography (TEG) and ROTEM thromboelastometry (TEM)) require clean, stable and vibration-free environments to properly validate their measurements. Coagulation assessment can take up to an hour using these instruments. Entegrion has developed an alternative to these devices that will perform the necessary testing in a portable environment suitable for far forward and patient transport arenas. Use of this device will allow surgeons in level 1, 2, or 3 hospitals to make medical decisions based on the accepted state of a patient's coagulation profile.

The project objective is to develop a hand-held, portable thromboelastograph for 510(k) submission. Entegrion has designated the device as the *Portable Coagulation Monitor* (PCM). This is a four-year project, and this report summarizes progress to date at the end of year three (Y3).

The overall Project Timeline as revised is:

1. Prototype Design, Testing, Validation – 12 months
2. Formal definition of Design Requirements & Specification – Months 13-15
3. Product Design & Development – Months 16-38
4. Certification Testing and Subsystem Design Corrections if needed-Months 25-47
5. Manufacturing Documentation – Months 42-47
6. FDA 510(k) Submission – Month 48

The activities comprising this project and the progress toward completion are set forth in the schematic below.

Task	Year 1 (2011)				Year 2 (2012)				Year 3 (2013)				Year 4 (2014)				Status
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
1a																	Complete
1b																	Complete
1c																	Complete
1d																	Complete
1e																	Continuing
1f																	Complete
1g																	Continuing
1h																	Continuing
2a																	Complete
2b																	Complete
2c																	Continuing
2d																	Continuing
3a																	Continuing
3b																	Continuing
3c																	Continuing
3d																	Continuing
3e																	Continuing
3f																	Complete
4a																	Delayed
4b																	Delayed
4c																	Delayed
4d																	Delayed
5a																	Complete
5b																	Complete
5c																	Complete
5d																	In Progress
6a																	Delayed
6b																	Delayed
6c																	Delayed
6d																	Delayed

BODY

The objective is to develop a prototype hand-held portable device that replicates the user interface and basic functionality of commercially available thromboelastographic systems (TEG and ROTEM), but with greatly improved portability. A 510(k) premarket notification seeking market clearance for the device will be submitted to the FDA for clearance. The secondary objective is to decrease the sample analysis time and to improve the range of coagulation assessments possible over existing commercially available technologies.

Year 1 work was centered on designing production-based units and testing the Portable Coagulation Monitor (PCM) internal design. Year 2 work was centered on manufacturing the units designed in Year 1 and improving the manufacturing process of the cassettes to ensure a repeatable method. Activity in Year 3 focused on completion of manufacturing and initial testing of prototype handheld PCM device, and preparation and planning for final verification and validation testing, including clinical and reference range studies in which PCM viscoelastic measurements of fresh whole blood samples will be compared with measurement results produced by the Rotem Natem assay using the same samples. During Year 3 Contractor requested a no cost extension of time to complete the project because of more stringent than anticipated FDA requirements and identified modifications needed to the device as testing began. Modifications to certain elements of the product are expected to be ongoing as the results of validation and verification are evaluated. These dynamics are typical in the development of diagnostic medical devices.

FIGURE 1: Portable Coagulation Monitor (PCM)

Task 1: Portable Coagulation Monitor (PCM) V2.0 Prototype Development, Testing and Validation:

Subtask 1a: Establish electro-mechanical performance limits: dynamic range of motors
Subtask 1b: Ability to integrate a disposable sample cassette
Subtask 1c: Test protocols for coagulation at low, intermediate, and high shear rate
Subtask 1d: Robustness of device architecture: 1 meter drop test

Subtasks 1a – 1d are complete. The voice coil actuator (VCA) motors will generate a physical displacement of 0.5 mm in each direction at 1 Hz and 0.030 mm in each direction at 100 Hz. The cassette design enables the wicking of blood into the 75 µ gap between the two glass plates. A shear rate of 1000/s was chosen based on the data. A one-meter drop test was conducted in-house on a prototype model, and there was no indication of damage and was found to comply with IEC 61010-1. Currently, loss of calibration has not been evaluated, and it is recommended that the device calibration be re-evaluated for compliance after such a drop. Further testing will be carried out on a manufactured model.

FIGURE 2: Disposable Cassette

Subtask 1e: Basic data analysis to emulate commercially available TEG and ROTEM systems

Entegrion in conjunction with its technical development subcontractors continues to refine the algorithms used to measure and display the results from samples of various test materials in preparation for testing of human blood. The completion of this task has been delayed due to difficulties with cassette and device manufacturing. Testing has been ongoing as engineering and software improvements with the PCM are being successfully implemented.

Subtask 1f: Basic user interface verification.

This task is complete. The display emulates the output of a ROTEM. The data is written to a micro-SD card that is embedded on the test cassette. This cassette can then be reinserted into the PCM device, and the data can be retrieved and saved to a computer via a USB interface. The graphic display has been programmed to resemble the ROTEM graphic output as see in Figure 3.

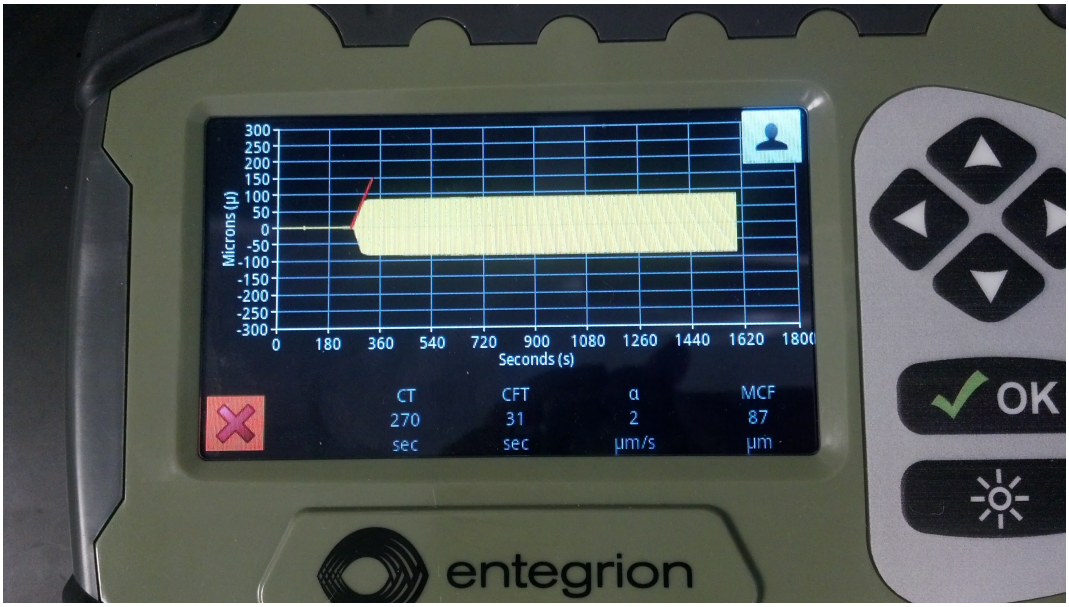

FIGURE 3: PCM Graphic Output

Subtask 1g: Blood sample temperature during test

Temperature has been observed during testing, and internal temperatures of approximately 30ºC have been observed without any controls running when PCM unit is operating in a lab environment with ambient temperatures of approximately 20ºC. The product has been tested in a 37ºC (desired temperature) chamber with no observable difference from units tested at 20ºC. Contractor expects to incorporate a mechanism for temperature control prior to clinical testing and filing of 510(k) to ensure operating stability of the device and control of variables affecting samples.

Subtask 1h: Benchmark: quantitatively assess PCM vs. ROTEM on matched samples of whole blood

Task is delayed due to cassette and device manufacturing issues. Preliminary comparisons have been made between PCM and Rotem during initial evaluation of prototype PCM devices. Testing will continue through the verification and validation phase that includes clinical study.

Task 2 - Formal definition of Design Requirements and Design Definition

Subtask 2a: Numbered Traceability as required by FDA.
Subtask 2b: Formal System Specification Documentation

These tasks were reported as complete. Numbered traceability and specifications documentation will be updated for any final modifications after the final device review is complete.

Subtask 2c: Device Hazard Analysis, failure modes and countermeasures
Subtask 2d: Formal Design Review at the completion of all subtasks under Task 2

Device Hazard Analysis, failure modes, and countermeasures and Formal Design Review have been delayed due to the review of the device algorithm evaluation across devices. Review is on going and expected to be complete in Year 4 – Q13.

Task 3 - PCM Product Design and Development
Subtask 3a: Refine PCM design for manufacturability and compliance

Significant improvements for manufacturability have been completed for the disposable cassette component of the device. Certain cassette modifications based on motion studies resulted in improvements in ease of use, accuracy of sample loading, and significant reduction in risk of contamination of operator and PCM device. Ongoing evaluation of design form manufacture of the analyzer component of the PCM will incorporate changes currently being evaluated for temperature control, ease of cleaning, secure coupling with disposable cassette, and other matters. Scheduled to be complete Y4, Q14.

Subtask 3b: Detailed evaluation of electronic design

Initial phase has been completed using bench top prototypes. Study reports will be updated to incorporate any modifications resulting from other subtasks within this major Task 3.

Subtask 3c: Formal release of Design Documentation

Original Design Documentation released. Will updated to incorporate any modifications resulting from other subtasks within this major Task 3.

Subtask 3d: Establishment of Integration Reports

This subtask has been completed in connection with the initial prototypes, and will be updated following completion of this major Task 3.

Subtask 3e: In-house testing prior to certification testing

Substantial testing of the prototypes has been conducted by Contractor, and by several subcontractors. Testing will continue as modifications being identified in this major Task 3 are implemented. Expect completion in Year 4, Q14.

Subtask 3f: Military Standards testing

All aspects of the device were designed in accordance with Military Standards.

Task 4 - PCM Certification Testing
Subtask 4a: IEC 60601-1
Subtask 4b: IEC 60601-1-2
Subtask 4c: ISO 10993
Subtask 4d: ISTA 2A

These tasks are delayed due to modifications being made to the device. Expected to be completed mid-Year 4.

Task 5 - Manufacturing Documentation
Subtask 5a: Device assembly drawings
Subtask 5b: Manufacturing assembly instructions
Subtask 5c: Wire and cable harness drawings
Subtask 5d: System Service Manual (English)

Device assembly drawings, manufacturing assembly instructions, and wire and cable harness drawings are completed for the initial build. Documentation will be updated for modifications to the device. The service manual is drafted and will be updated as needed based on results of verification and validation.

Task 6 - FDA 510(k) clearance
Subtask 6a: Completed Design Portfolio, CFR 812 compliant
Subtask 6b: Finalized comparison with predicate devices
Subtask 6c: Written response from FDA
Subtask 6d: Clearance letter (510(k)) from FDA

FDA strongly recommended an additional reference range study be conducted prior to 510(k) filing in addition to increasing the subject size of the initially proposed clinical trial. A second meeting with the FDA will be held during the first half of Year 4 to review Contractor's updated testing plans and understand any changes in the FDA's views toward evaluating diagnostic devices in this area. The submission of the 510(k) is planned by the end of Year 4.

KEY ACCOMPLISHMENTS

- Eight additional test units with improved electronics completed and tested
- Improved software for PCM/PC interaction
- Technical improvements to handheld device and disposable cartridge were identified based on initial testing, and implementation began, including:
    - Modifications of the disposable cartridge for manufacturability, reliability, ease of blood sample loading, and reduction of contamination risk
    - Software improvements for controlling key PCM analyzer functions
    - Improved protocol for storing test results, removing circuitry from disposable cartridge in favor of storage within PCM analyzer unit (improving reliability and flexibility of data transmission options).
- Development of verification and validation plan based on regulatory input and recognized device development standards

REPORTABLE OUTCOMES

- Presentation of PCM development program to Military Health System Research Symposium August 2013

CONCLUSION

Year 3 of the project involved substantial progress in advancing the prototype PCM device into a diagnostic instrument, as well as design improvements for ease of use, safety, and manufacturability. Clarification of verification and validation strategy is expected to facilitate filing of 510(k) with the FDA by the end of Year 4.

REFERENCES

None

APPENDICES

None

SUPPORTING DATA

None